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Is Endoscopic Drainage Better than Percutaneous Drainage for Patients with Pancreatic Fluid Collections? A Comparative Meta-Analysis

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ABSTRACT

Introduction
Though endoscopic and percutaneous drainage has emerged as the most common minimally invasive treatments for Pancreatic fluid collections (PFCs), estimates of therapeutic superiority of the two treatments have yielded inconsistent results.

Methods
We retrieved studies compared the efficacy and safety of the two approaches in PubMed, Embase, and the Cochrane Library. Primary outcomes were differences in technical success, clinical success and adverse events, and the secondary outcomes were differences in reintervention, the need for surgical intervention, mortality, recurrence and length of hospital stay.

Results
There were nonsignificant differences in technical success rate (OR, 0.54; CI, 0.15–1.86), clinical success rate (OR, 1.39; CI, 0.82–2.37), adverse events rate (OR, 1.21; CI, 0.70–2.11), mortality rate (OR, 0.81; CI, 0.30–2.16), and recurrence rate (OR, 1.94; CI, 0.74–5.07) between the two groups. The reintervention rate (OR, 0.19; CI, 0.08–0.45) and the proportion of the need for surgical intervention (OR, 0.08; CI, 0.02–0.39) in the endoscopic drainage group were much lower than those in the percutaneous drainage group. The total length of hospital stay (SMD, -0.60; CI, -0.84 to -0.36) in the endoscopic drainage group was shorter, however, there was a nonsignificant difference in the length of post-procedure hospital stay (SMD, -0.30; CI, -1.05–0.44) between the two groups.

Conclusion
Endoscopic drainage is effective for PFCs with the superiority in less reintervention and less surgical need over traditional percutaneous drainage, despite the similar clinical efficacy and safety compared with traditional percutaneous drainage.

Keywords
Endoscopic drainage; percutaneous drainage; pancreatic fluid collections; meta-analysis.
INTRODUCTION
Pancreatic fluid collections (PFCs) are common local complications of acute or chronic pancreatitis, pancreas injury or pancreatic surgery which can cause abdominal pain, gastrointestinal obstruction or intra-abdominal infection. While the prevalence of PFCs is around 40% of patients with acute pancreatitis, the disease is spontaneous remissive in most of them. According to the revised Atlanta classification, PFCs can be classified into the following 4 types: in the absence of pancreatic or peripancreatic necrosis, the collections existing shorter and more than 4 weeks are called acute peripancreatic collection (APC) and pancreatic pseudocyst (PP) respectively; in the presence of pancreatic necrosis, the collections existing shorter and more than 4 weeks are called acute necrotic collection (ANC) and walled-off necrosis (WON) respectively. When patients with symptomatic mature PFCs that is progressing into infectious PFCs or with a constant increase in size during a follow-up, intervention treatments should be recommended. The traditional treatment for symptomatic PFCs is surgical drainage. However, it is more traumatic, especially for the patients with massive necrotic collection, with a higher incidence of complications and mortality. In recent years, with the development of minimally invasive technology, interventional therapies represented by endoscopic drainage and percutaneous drainage have been widely used in the treatment of PFCs. Surgery is just used as a remedy when other treatments have failed or serious complications have occurred. The characteristics of endoscopic therapy are no external drainage catheter, no external pancreatic fistula, less loss of body fluid and electrolytes. Yet there is still no clear consensus on which has better efficacy and safety for PFCs while comparing percutaneous drainage and endoscopic drainage. When comparing these two interventional therapies, studies report inconsistent results which are limited by their relatively small sample size. Therefore, we conducted a systematic review and meta-analysis in order to compare the efficacy and safety between endoscopic drainage and percutaneous drainage in patients with PFCs.

METHODS
Search strategy
Relevant studies in PubMed, Embase, and the Cochrane Library were retrieved from their inception to March 2020. References on the same topic were traced back to their sources and included in our meta-analysis by manual searches at the same time. Subject headings and non-controlled terms were combined in each retrieval. The key MeSH terms used in database searches were as follows: (“endoscopic” OR “EUS-guided” OR “endoscopic ultrasound-guided”) AND (“percutaneous drainage” OR “percutaneous catheter drainage”) AND (“pancreatic fluid collection” OR “pancreatic fluid collections” OR “peripancreatic fluid collection” OR “peripancreatic fluid collections” OR “acute peripancreatic fluid collection” OR “acute necrotic collection” OR “necrotizing pancreatitis” OR “infected pancreatic necrosis” OR “pseudocysts” OR “pancreatic pseudocyst” OR “walled-off necrosis” OR “walled-off pancreatic necrosis”). The inclusion criteria were defined as: 1) randomized controlled trials (RCTs) or cohort studies 2) comparing the efficacy and safety between endoscopic drainage and percutaneous drainage in patients with PFCs 3)
the outcome should include at least one of the following indices: technical success rate, clinical success rate and adverse event rate; and 4) studies with adults, 5) published in English. The exclusion criteria were as follows: 1) studies with unavailable data or valid data that could not be extracted, or 2) duplicately published; or 3) unavailability of full-text articles.

Data extraction
Studies were screened and extracted by two researchers (QCC and YXZ) independently and cross checked for accuracy. Any disagreement was settled through discussions or consultations with a senior researcher (BX). In the process of literature screening, firstly, obviously irrelevant studies were removed after we read titles and abstracts. Secondly, we read the full texts of the remaining articles and included eligible ones. The uncertain but very important information was obtained by contacting the author by email or phone as much as possible. Thirdly, data consisting of basic information (title, the first author, country, publication year, research type, cases of patient, age, gender, etc.), baseline characteristics and interventions for subjects, key items in biased risk factor assessments, and outcomes measurement information were extracted from included studies.

Outcomes
Primary outcomes encompassed technical success rate, clinical success rate, adverse events rate, and the secondary outcomes were reintervention rate, rate of the need for surgical intervention, mortality rate, recurrence rate, and length of hospital stay. Technical success is defined as success to place a stent or catheter to PFCs and the ability to discharge PFCs. Clinical success is defined as clinical improvement which means resolution of PFCs in radiographic improvement without need for surgery. Reintervention is defined as need for repeatable procedures due to persistent symptoms or persistent PFCs on follow-up imaging. Recurrence is defined as reappearance of PFCs after disappearance with a successful primary drainage.

Quality assessment
For observational studies, the New Castle Ottawa scale (NOS)(10) recommended by the Cochrane collaborative network was used for quality assessment. The NOS scale mainly comprised three indicators: the selection of research population (four items, one star for each item), the comparability between groups (one item, two stars at most), and outcomes measurement (three items, one star for each item). The full score was 9 points, studies with more than 7 points could be considered as high-quality, with 5-7 points as medium-quality, and with less than 5 points as low-quality. Two researchers scored all included studies according to the predetermined standard scheme. Any disagreement on the scores that could not be solved by discussion would be settled by the third researcher.

Statistical analysis
This meta-analysis was carried out using Stata 14.0. Odds ratio (OR) was used as the effect size for counting data and mean difference (MD) or standard mean difference (SMD) as the effect size for measuring data, with 95 % CI provided for each effect. The length of hospital stay was presented as mean ± SD which was provided directly
or calculated according to estimates of sample size, median, range and/or interquartile range indirectly, cited from Dehui Luo (2018)(11). The heterogeneity among the results was judged by Cochrane Q test (the inspection level of $\alpha = 0.1$), and the size of heterogeneity was quantitatively determined by combining with $I^2$ (0-50% of $I^2$ indicated no significant heterogeneity, 51-75% of $I^2$ moderate heterogeneity, and 76-100% of $I^2$ high heterogeneity). A fixed-effect model was used for the meta-analysis when there was no statistical heterogeneity among the results, and the source of heterogeneity required further analyses when there was statistical heterogeneity among the results. After studies showing obvious influences on the clinical heterogeneity were removed, a random-effect model was adopted. Salient clinical heterogeneity was handled by a subgroup analysis or sensitivity analysis, or only a descriptive analysis. A funnel plot was used to determine whether there was publication bias. A $P$ value of less than 0.05 was considered statistically significant.

RESULTS
Baseline characteristics and quality assessment
According to the retrieval strategy, 687 articles were found, and 372 were left after eliminating the duplicated literature. After two researchers read titles and abstracts, 286 unrelated studies were excluded. Furthermore, 75 studies were ruled out after the two researchers read full texts of the rest 86 articles. Finally, 11 articles(12-22) representing 297 patients in the endoscopic drainage group and 253 in the percutaneous drainage group were included in our meta-analysis. A detailed PRISMA flow diagram is shown in Fig 1. All 11 articles were cohort studies, consisting of 9 (12-14, 16, 18-22) retrospective studies and 2 (15, 17) prospective studies. Five (12, 15, 16, 21, 22) of them reported patients with post-operative PFCs and six (13, 14, 17-20) reported PFCs related to pancreatitis. The characteristics of eligible studies are shown in Table 1. The scores of NOS scale indicated that all studies were medium- to high-quality. (Table 2).

Meta-analysis results
Technical success
7 studies(12, 13, 15, 16, 20-22) compared technical success rates of the two approaches, while 3 studies(12, 13, 21) were excluded because data cannot be calculated. There was no significant heterogeneity among them (Cochrane Q test: $P = 0.491$, $I^2 = 0 \%$); No statistically significant difference in the technical success rate was found between endoscopic drainage and percutaneous drainage (OR, 0.54; 95 % CI, 0.15–1.86) (Fig. 2A).

Clinical success
The meta-analysis for 9 studies(12, 13, 15-18, 20-22) on the clinical success rate of the two approaches was conducted. A random-effect model showed that there was a nonsignificant difference in clinical success between the two drainages (Cochrane Q test: $P = 0.020$, $I^2 = 56.1 \%$; OR, 1.98; 95 % CI, 0.97–4.07) (Fig. 2B). The funnel plot (Fig. 3A) and Begg’s test showed no publication bias among the studies ($P = 0.902$). To trace origin of heterogeneity, a sensitivity analysis was performed and the result showed that the study by Keane 2016(18) had a significant impact on heterogeneity. The remaining 8 studies had no heterogeneity after eliminating each one of them.
(Cochrane Q test: $P = 0.420, I^2 = 1.3\%$). The meta-analysis for the 8 studies showed that there was still no statistically significant difference in clinical success between endoscopic drainage and percutaneous drainage (OR, 1.39; 95 % CI, 0.82–2.37) (Fig. 2C).

**Adverse events**

8 studies (13, 15-20, 22) compared the reporting rates of adverse events between the two types of drainages, while one study (16) was excluded because data cannot be calculated. There was a nonsignificant difference in the reporting rate of adverse events between the two treatments (Cochrane Q test: $P = 0.229, I^2 = 26.2\%$; OR, 1.21, 95 % CI 0.70–2.11) (Fig. 2D). The result was stable because the sensitivity analysis of the 8 articles showed that none of them had a great impact on each other. The funnel plot (Fig. 3B) and Begg’s test showed that there was no publication bias in these studies ($P = 0.881$).

**Reintervention**

The meta-analysis of 3 studies (12, 13, 20) that compared the rate of reintervention between the two approaches was carried out. There was no significant heterogeneity among them (Cochrane Q test: $P = 0.240, I^2 = 30.0\%$). The rate of reintervention in the endoscopic drainage group was significantly lower than that in the percutaneous drainage group (OR, 0.19; 95 % CI, 0.08–0.45) (Fig. 2E).

**The need for surgical intervention**

The meta-analysis of 3 studies (13, 14, 17) reporting the rate of surgical need between the two groups was performed. There was no significant heterogeneity among them (Cochrane Q test: $P = 0.931, I^2 = 0\%$). The rate of surgical need in the endoscopic drainage group was significantly lower than that in the percutaneous drainage group (OR, 0.08; 95 % CI, 0.02–0.39) (Fig. 2F).

**Mortality**

6 studies (13, 14, 16-19) reported mortality after the two interventions, while 2 studies (13, 16) were excluded because data cannot be calculated. There was a nonsignificant difference in mortality between the two approaches (Cochrane Q test: $P = 0.114, I^2 = 49.5\%$; OR, 0.81; 95 % CI, 0.30–2.16) (Fig. 2G).

**Recurrence**

Five studies (13, 15, 17, 18, 22) were included in the meta-analysis for the recurrence after drainage, which showed a moderate heterogeneity among them (Cochrane Q test: $P = 0.072, I^2 = 53.5\%$). The pooled OR was 1.11, with the corresponding 95 % CI ranging from 0.31–3.94. (Fig. 2H). The Begg’s test revealed that there was no publication bias in these studies ($P = 0.806$). We performed a sensitivity analysis because 1 study (13) seem to be an outlier, but the result didn’t alter after ruling out this study (OR, 1.94, 95 % CI, 0.74–5.07) (Fig. 2I). Therefore, there was a nonsignificant difference in recurrence after drainage between endoscopic drainage and percutaneous drainage.

**Length of hospital stay**
Ten studies (12-20, 22) comparing the length of hospital stay between the two approaches was included in this meta-analysis, which had a significant heterogeneity among them (Cochrane Q test: $P = 0.000$, $I^2 = 83.7\%$). The sensitivity analysis was performed to trace origin of heterogeneity and revealed that the study from Keane 2016(18) had a great impact on heterogeneity. After excluding the study, a random-effect model was used in the following meta-analysis which showed that there was a statistically significant difference in the length of hospital stay between the two approaches (SMD, -0.56; 95% CI, -0.91 to -0.21) (Fig. 2J). The funnel plot (Fig. 3C) and Begg's test showed no publication bias in these studies ($P = 0.076$). Subsequently, a subgroup analysis was conducted for more details. The subgroup meta-analysis for the total length of hospital stay showed that the length was significantly shorter in the endoscopic drainage group than that in the percutaneous drainage group (Cochrane Q test: $P = 0.104$, $I^2 = 45.2\%$; SMD, -0.60; 95% CI, -0.84 to -0.36) (Fig. 2J). The subgroup meta-analysis for the length of post-procedure hospital stay showed that there was a nonsignificant difference between endoscopic drainage and percutaneous drainage (Cochrane Q test: $P = 0.050$, $I^2 = 66.7\%$; SMD, -0.30; 95% CI, -1.05–0.44).

**DISCUSSION**

In our findings, while endoscopic drainage and percutaneous drainage have comparable efficacy and safety, endoscopic drainage shows the superiority of lower reintervention rate and less need for surgical intervention over percutaneous drainage. A meta-analysis conducted by Mohan et al. (23) compare the efficacy and safety of the two methods for postoperative PFCs and yield the result that endoscopic drainage exhibits a higher clinical success rate than percutaneous drainage. Obviously, scientific evidences in our meta-analysis are stronger as most included studies in Mohan’s analysis are merely single-arm studies while ours is a comparative meta-analysis. Moreover, our study may have more clinical value since postoperative PFCs constitute a very small population. Another similar meta-analysis conducted by Khan et al. (24) conclude that endoscopic drainage has better clinical success (RR, 0.40, 95% CI, 0.26–0.61). Unfortunately, this meta-analysis includes fewer outcomes and fewer studies, and not all included studies compare the two methods directly, which cannot be comparable to ours in detailed contents and scientific evidences.

According to our meta-analysis, there is no significant difference in technical success and clinical success rate between these two approaches. A subgroup meta-analysis still shows no difference between postoperative subgroups in clinical success, which is different from Mohan’s result. But with the continuous development of stents and endoscopic skills, we are looking forward to the emergence of such advantages from endoscopic drainage. Moreover, endoscopic drainage is able to solve some problems, such as pancreaticolithiasis, stenosis of pancreatic duct and choledocholithiasis, which cannot be solved by percutaneous drainage.

Adverse events occur commonly with both approaches, while no difference is found between them. Generally, major complications are bleeding, intense pain, infection, stent or catheter migration, pancreatic fistula, visceral perforation. Bleeding intra endoscopic procedure can be controlled by balloon compression under endoscopic guidance, and bleeding after procedure can be resolved by hemostatic drugs,
radiologic embolization and emergency operation. After percutaneous drainage, the infectious patients should be treated with anti-infective therapy and changed to a new catheter(13). The reintervention rate after percutaneous drainage is much higher, which may be related to the patency of drainage position. Incidences such as a collapsed PFC drainage site and catheter displacement and blockage resulting from an improper management after discharge requires reinterventions(25). Multiple stents can be placed side by side guided by endoscope, advantageously ensuring the patency of drainage(20, 26). Moreover, endoscopic drainage aids in draining out necrotizing tissue that contains solid fragments, which is impossible for a percutaneous drainage catheter with a small diameter. Endoscopic drainage featuring more thorough drainage and durable service achieves a lower reintervention rate and recurrence rate in clinical practices.

In our findings, endoscopic drainage need less surgical intervention. As we know, patients with bleeding, perforation, unsatisfied drainage efficacy of necrotic collection require additional surgical intervention. Therefore, we guess that endoscopic therapy may have less risk of bleeding and perforation, and it is more advantageous for infected pancreatic necrosis (IPN) patients. More studies are needed to confirm this.

The overall mortality after each method is low and no difference is found between them. For instance, two studies(13, 16) are excluded when pooling data due to no death in both groups. As Woo et al.(14) reported, there were two deaths in the endoscopic group and one death in the percutaneous group. The most frequent causes of death are septic shock, respiratory failure and colonic fistula(27). Therefore, for sever patients, timely intervention is of much importance.

Recurrence of PFCs is common after both methods and no difference is found between them. After disappearance of PFCs with a successful primary drainage, almost 20% patients will relapse(28). There were four patients who experienced recurrence of their PFCs in Efishat’s report(15). Two of them were treated with conservative therapy, and another two were treated with a repeatable endoscopic debridement and drainage. All patients got successful drainage and no recurrence again on follow-up imaging.

There are two subgroups of length of hospital stay, the total length of hospital stay and the length of post-procedure hospital stay, in our meta-analysis. The results show that the total length of stay following endoscopic drainage is much shorter than that after percutaneous drainage, but the length of post-procedure stay after the two drainages is similar in the comparison of the two approaches. As all the included studies are not RCT trials, along with the absence of clinical guidelines, the treatment strategies based on the preferences of clinician may result in some selection bias.

Although percutaneous drainage is a traditional treatment for PFCs, external drainage catheter requires long-term care and maintenance, which not only affects the quality of life of patients but also poses risks of local skin infection and external pancreatic fistula(29). Therefore, endoscopic drainage has become a research hotspot in recent decade. Albers et al.(30) focus on the treatment of infected pancreatic necrosis (IPN); combining endoscopic-ultrasound guided drainage, stent, lumenal debridement and percutaneous drainage, they report that there are 12 out
of 13 patients achieved sustained clinical success after an average follow-up of 8.5 ± 5.9 months. A recent meta-analysis is also in favor of endoscopic approach for IPN(31). Gluck et al.(32) show that comparing with mere percutaneous drainage, the combination of endoscopic drainage and percutaneous drainage can significantly reduce the length of hospital stay (55 days vs. 26 days) for PFCs. According to a recent cohort study, endoscopic drainage is also used for other abdominal abscesses, which exhibits the same efficacy with the same incidence rates of recurrence and adverse events as percutaneous drainage(33). Inamdar et al.(34) report that endoscopic drainage should be enrolled in the first-line treatments for patients with malignant biliary obstruction because its reporting rate of adverse events is much lower than that of percutaneous drainage. Unfortunately, our meta-analysis did not find such an advantage over adverse events in endoscopic drainage. More studies are paying attentions to the selection of stents in endoscopic drainage. Compared with plastic stents, metal stents with a large diameter (≥ 15 mm) can simplify procedures and reduce bleeding risks(35, 36). Chen et al.(37) report that the drainage success rate in patients using metal stents is higher (92 % vs. 84 %) despite the corresponding higher costs. For necrotizing pancreatic collection, a “step-up” therapy based on minimally invasive procedures is recommended currently(38, 39). Therefore, our further study series focus on screening out the optimal minimally invasive approach, which is the priority, for the drainage for pancreatic diseases. One of the possible research directions is whether the initial selection of minimally invasive intervention, endoscopically or percutaneously, affects the subsequent surgical treatment, if necessary, and the long-term prognosis for patients.

On the whole, endoscopic drainage treatment is a better choice, but the treatment for PFCs should be personalized. If the anatomic location of collection permits draining into the stomach or duodenum directly, endoscopic approach will be the first choice. But if collection extends to the paracolic sulci or pelvic cavity, combination of both methods is probably the best approach(40). Therefore, prior CT evaluation is very useful for reference. Endoscopic drainage treatment requires general anesthesia, which means for those with serious complications or who cannot tolerate anesthesia percutaneous drainage also has its own advantages. However, for most patients calling for continuous drainage after discharge, beauty and quality of life are issues to be considered, which is a distinct disadvantage of percutaneous drainage. For severe patients with complicated conditions, a combination of multiple methods is required. Especially when PFCs are located in retroperitoneal, combination of both methods can avoid open surgery in many cases(41).

One of the advantages of this study is that there is no significant publication bias. However, the limitations of this study should be clearly acknowledged. Firstly, since no RCT on this topic has been published, all included researches are cohort studies. The evidence level is not strong enough. More prospective, large-sample RCTs are needed for further studies. Secondly, the length of follow-up in the majority of included studies is short and various, which may affect the accuracy of the results. Thirdly, partial means and standard deviations were provided indirectly, which may have introduced bias. Fourthly, all literature included are in English so there may be language bias.

CONCLUSIONS
In conclusion, endoscopic drainage is effective for PFCs, with the superiority in less reintervention and less surgical need over traditional percutaneous drainage, despite the similar clinical efficacy and safety. The continuous progress of endoscopic technique and stents will shed light on the prospect of endoscopic drainage in better treatment for PFCs, which needs to be identified in more large-sample RCTs.

REFERENCES


Table 1. Main characteristics of the eleven included studies

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<th>Age</th>
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*Data are presented as mean ± SD *Data are presented as median with range. *Data are presented as median with IQR. *Data are presented as mean

Table 2. Quality assessment of included studies
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Figure 1. Flow chart of study selection process according to the PRISMA statement.
based on sensitivity analysis. J. Length of hospital stay. (OR: odds ratio; SMD: standard mean difference; LOS: length of hospital stay).

Figure 3. Funnel plot of two interventions for outcomes. A. Clinical success. B. Adverse events. C. Length of hospital stay. (OR: odds ratio; SE: standard error).